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With warm regards
Lily

Some nitpicks

Selling Pure Science in Wartime: The Biochemical Genetics of G. W. Beadle

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To historians of the life sciences, geneticist George Wells Beadle is best known for his outstanding contributions to fundamental knowledge in molecular biology, research that linked formalistic concepts of classical genetics with material, or biochemical, explanations. His program of biochemical genetics, which he developed at Stanford University with biochemist Edward L. Tatum during the war years (1940—1945) replaced the fruit fly *Drosophila* — the most important system of classical genetics — with the bread mold *Neurospora crassa*, a simple microorganism amenable to genetic investigations on the biochemical level. By utilizing the *Neurospora* system Beadle was able to solve a central problem in heredity research, a problem that had been a focus of ongoing debate since the first decade of the twentieth century. This debate centered about the relationship between genes and enzymes: whether genes ~~were~~ enzymes, or whether they only *made* enzymes. Beadle demonstrated that one gene controlled only a single biochemical ~~reaction~~, which, in turn, was regulated by one specific enzyme; this relationship was enunciated in the early 1950s as the "one gene—one enzyme hypothesis," a fundamental principle in molecular biology.[1]

In addition to its intellectual import, Beadle's work has also been acclaimed by historians of science and by scientists as a ...

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1. For accounts of Beadle and biochemical genetics, see J. S. Fruton, *Molecules and Life* (New York: John Wiley and Sons, 1972), chap. 3; R. C. Olby, *The Path to the Double Helix* (London: Macmillan, 1978), chap. 2; H. F. Judson, *The Eighth Day of Creation* (New York: Simon and Schuster, 1979), chap. 7; F. H. Portugal and J. S. Cohen, *A Century of DNA* (Cambridge: MIT Press, 1977), chap. 8; N. H. Horowitz, "Genetics and the Synthesis of Proteins," *Ann. N. Y. Acad. Sci., 325* (1979), 253—266; and L. E. Kay, "Cooperative Individualism and the Growth of Molecular Biology at the California Institute of Technology, 1928—1953," Ph.D. diss., The Johns Hopkins University, 1986, chaps. 3 and 6.

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— started with Drosophila 1937.
Neurospora began 1941.

He never demonstrated that (nor that gene was not an enzyme) He asserted a 1:1 relationship, never critically analyzed what it meant except that "genes control enzymes" in some direct way — and did initiate marvellous experimental methods to study how genes do act! But Beadle never isolated an enzyme, nor dissect how a gene effects its formation.

major disciplinary innovation. *Neurospora* research brought together two areas in the life sciences that in the United States had previously been remote: genetics and biochemistry. Because American genetics had been shaped to a large extent by its service-role to agricultural sciences — plant and animal breeding — while biochemistry developed mainly within a medical context, these two fields represented very different scientific traditions, with dissimilar vocabularies and laboratory training. In fact, until the mid-1940s, biochemists (and physiologists) by and large ignored genetics. Researchers in several areas in the life science including embryology and cytology, tended not to acknowledge the physical existence of genes, viewing them as mere theoretical constructs of the geneticists' lore. Beadle's research program forged the first intellectual and institutional links between these two disciplines in America.[2]

Beadle's ascent within the scientific hierarchy was commensurate with his accomplishments. He was elected to the National Academy of Sciences in 1944, and in 1945, shortly after the end of the war, he moved, or rather returned, to the California Institute of Technology to lead an enormous program in molecular biology. In 1958, Beadle and Tatum were awarded the Nobel Prize in Physiology (shared with Joshua Lederberg) for demonstrating that genes regulate definite chemical processes.[3]

Historians of the life sciences, however, have completely ignored the time-frame of Beadle's research program, which paralleled World War II. Indeed, what makes Beadle's rise to scientific leadership so remarkable is the fact that the research in *Neurospora* genetics was launched at the end of 1940, just at the height of the "preparedness period" — the phase of scientific mobilization pre-

2. On the intellectual gulf between genetics and biochemistry see, for example, H. Fraenkel-Conrat, "Protein Chemists Encounter Viruses," *Ann. N. Y. Acad. Sci., 325* (1979), 309—318. On the agricultural context of biology in general and genetics in particular see C. E. Rosenberg, "Science, Technology, and Economic Growth: The Case of the Agricultural Experiment Station Scientist, 1875—1914" and "The Social Environment of Scientific Innovation: Factors in the Development of Genetics in the United States," in *No Other Gods* (Baltimore: The Johns Hopkins University Press, 1978), pp. 153—172, 196—209. On the medical context of biochemistry see R. E. Kohler, *From Medical Chemistry to Biochemistry* (Cambridge: Cambridge University Press, 1982). We shall see later that the University of Wisconsin was an important exception: there biochemistry developed within a context that linked agriculture and medicine through nutrition and pharmacology.

3. For description of the prize-winning works, Nobel addresses, and biographical information, see "1958: G. W. Beadle, E. L. Tatum, and J. Lederberg," *Nobel Lectures in Molecular Biology, 1933—1975* (New York: Elsevier North-Holand, 1977), pp. 352—368.

ceding America's entry into the war. His program reached its zenith — in terms of funding and personnel — in 1943, at a time when most fundamental researches were being cut back. While national resources were being diverted toward war-related projects and scientists had to interrupt their basic research, Beadle's program in biochemical genetics flourished. The bulk of the work for which Beadle and Tatum received the Nobel Prize was accomplished during the years 1941—1945. If we also take into account that initially the theoretical implications of Beadle's experiments were by no means universally accepted, that in the 1940s his interpretations encountered skepticism among geneticists and biochemists, then his rise to scientific leadership under the exigencies of war becomes even more surprising. How did Beadle accomplish this scientific feat?

The answer to this question reveals an important, yet hitherto neglected, dimension in the history of molecular biology: the practical and commercial sides of basic research and their relation to the war effort. Beadle's remarkable success was the outcome of an astute two-tiered approach to biochemical genetics: the theoretical, and the applied. While his primary commitment was to fundamental biological knowledge — the relationship between genes and enzymes — he stressed from the beginning the potential commercial returns of *Neurospora* research. It was mainly because of its practical applications that his work received priority considerations during the war, thus ensuring the program's survival and growth. In tracing the development of Beadle's research program during the war years, we thereby attain a broader and more balanced view of the history of molecular biology. At the same time, this account also fills a lacuna in the historiography of the important relationships between American biological research, commercial applications, and military needs.

I. THE INTELLECTUAL MOTIVATION

When Beadle tackled the study of the relationship between genes and enzymes in *Neurospora* in 1940, one of the most urgent issues in biology was the connection between the structure of genes and their biological functions. Stated more specifically, the questions were: What are the chemical properties of genes and the physicochemical mechanisms by which they replicate, transmit hereditary traits, mutate, control development, and regulate physiological processes?

The mapping approach to genetics of Thomas Hunt Morgan's *Drosophila* school in the 1910s and 1920s had established the

linearity of genes in the chromosomes. By performing multitudes of Mendelian crosses of wild-type and mutant flies, using mutations as markers, the Morgan school had generated detailed genetic maps. These maps inferred the precise location of genes that were responsible for the transmission of particular visible traits, such as eye color, bristle type, or wing shape. Although the researches of the *Drosophila* school went beyond mapping — including also problems such as position effect, mutation, chromosomal rearrangements, multiple allelism, and chromosome evolution — these studies were done by purely genetic methods. The Morgan school had deliberately ignored the issue of the gene's material nature. Morgan felt that due to the complexities and the muddled thinking surrounding studies of the physicochemical mechanisms that led from genes to their physiological products (for example, from a gene that determined coat color to the development of actual pigment), it would be best for the time being to avoid the problem of material properties. In part as a result of the formalistic, nonphysical approach to heredity, most biochemists and physiologists in the 1930s regarded these inferred units — genes — as mere theoretical constructs of the geneticists. American geneticists, for their part, generally remained intellectually and institutionally isolated from biochemists and physiologists, even in areas of overlapping research interests, such as replication and development.[4]

Due to the confluence of several intellectual and institutional trends in the early 1930s — especially the emphasis by the Rockefeller Foundation on physicochemical biology — physiological and biochemical aspects of genetics began to attract young researchers from the life and physical sciences. Morgan, now chairman of the new biology division at the California Institute of Technology (which after 1931 included Beadle), became a zealous promoter of the new scientific agenda. Explaining what genes are and what they do in physicochemical language became a primary goal of the nascent discipline of molecular biology, especially at Caltech.[5]

4. T. H. Morgan, *The Theory of the Gene* (New Haven: Yale University Press, 1926); G. E. Allen, *Thomas Hunt Morgan* (Princeton: Princeton University Press, 1978); and N. Reingold I. Reingold, eds., *Science in America* (Chicago: University of Chicago Press, 1981), pp. 146—149.

5. For the role of the Rockefeller Foundation in the rise of molecular biology see R. E. Kohler, "The Management of Science: The Experience of Warren Weaver and the Rockefeller Foundation Programme in Molecular Biology," *Minerva, 14* (1976), 249—293; E. J. Yoxen, "Giving Life a New Meaning: The Rise of the Molecular Biology Establishment," in *Scientific Establishments and Hierarchies*: Sociology of the Sciences, ed. N. Elias, H. Martins, and R. Whitly

Beadle, raised and educated in the farmlands of Nebraska, came to Caltech in 1931 as a National Research Council Fellow already predisposed to the new interdisciplinary trends of physicochemical genetics. While completing his doctoral research in corn genetics at Cornell under Rollin A. Emerson, Beadle, at his mentor's suggestion, also audited courses in physical chemistry and biochemistry. It was a particularly exciting time to be involved in biochemistry, he later recalled, for the mid-1920s were the golden age of enzymology and Cornell was an important center, where biochemist John B. Sumner conducted his landmark research that led to the crystallization of the first enzyme (1926), and to his Nobel Prize.[6] Although Beadle began his research at Caltech within the classical framework of *Drosophila* genetics, his scientific imagination had already been captured by the biochemical puzzle of gene action, especially in relation to enzymology. There seemed to be a perpetual circularity about explaining the physiology of gene action. If one knew what a gene was, one could probably find out how it worked; if, on the other hand, one understood the mechanism of gene action, one could begin to predict what the gene was. The problem was to solve both at once while knowing neither.

A key issue within that circularity was the relationship between genes and enzymes. The confusion surrounding the gene-enzyme problem went back to the first decade of the twentieth century, to the rise of genetics and the beginnings of enzymology. It was suggested already then that phenotypic characters that were inherited according to Mendelian laws, such as color pigment in flowering plants, or coat color in animals, involved the action of oxidative enzymes. These early studies in physiological genetics had been conducted mainly in Europe. British physiologist J. B. S. Haldane, who in the 1930s was a visiting professor at Caltech and had a considerable influence on Beadle's thinking, had been expecially influential in establishing some of the early correlations between gene function and enzyme action. In fact, Haldane was responsible for calling attention to the classic 1909 work of the English physician Archibald Garrod, investigations that linked the inborn metabolic defect alkaptonurea — the excretion of dark

(Dordrecht: Reidel, 1982), IV, 123—143; P. Abir-Am, "The Discourse of Physical Power and Biological Knowledge in the 1930s: A Reappraisal of the Rockefeller Foundation's 'Policy' in Molecular Biology," *Soc. Stud. Sci., 12* (1982), 341—382; and L. E. Kay, "Conceptual Models and Analytical Tools: The Biology of Physicist Max Delbrück," *J. Hist. Biol., 18* (1985), 207—246.

6. G. W. Beadle, "Recollections," *Ann. Rev. Biochem., 43* (1974), 1—13.

urine — with the absence of an enzyme and, in turn, with the expression of a recessive Mendelian trait.[7]

This mere correlation, however, was interpreted by most researchers in the life sciences (including Haldane) to mean an identity relation. Most physiologists and biochemists — notably Jacques Loeb, Max Bergmann, and Richard Goldschmidt — postulated that genes were actually enzymes; that genes directly catalyzed the biochemical reactions that led to physiological products such as pigments, amino acids, and hormones. And although American geneticists in the 1920s generally did not concern themselves with these physiological and biochemical issues, those few geneticists who did, reached no clear-cut consensus, Morgan (and Alfred H. Sturtevant), for example, strongly disagreed with the premise that gene function could be equated with enzyme action. Morgan argued that the correlation between the action of enzymes and the presence of genes did not prove their identity, for an enzyme might be several stages removed from the gene. He insisted that until more rigorous studies were conducted, one could only speak of genes as some sort of protein bodies that somehow influenced the action of enzymes in the cytoplasm. Elucidating the precise nature of that influence became the target of Beadle's research program.[8]

During the years 1934—1940 Beadle, in a remarkably influential collaboration with French cytogeneticist Boris Ephrussi and a couple of other European biochemists, explored the physiology of gene action in relation to development through a series of transplantations of embryonic eye buds in *Drosophila* larvae. By using two well-characterized eye-color mutations — vermilion and cinnabar — as starting points, and then working out the biochemistry of eye-pigment synthesis, Beadle and his collaborators demonstrated that the normal brown eye pigment in the wild-type fly was synthesized in a stepwise fashion. Of the two steps that were examined, one turned out to be controlled by the vermilion gene, and one by the cinnabar gene. Although at the time Beadle and Ephrussi did not discuss the relation of the gene to the enzyme that regulated the corresponding biochemical step, the results of

7. On the early European studies in physiological genetics and the gene-enzyme problem see Olby, *Path to the Double-Helix*, chap. 8; Fruton, *Molecules and Life*, pp. 225—254; J. Harwood, "History of Genetics in Germany," *Mendel Newsl., 24* (1984), 1—4. For Haldane's contributions see N. W. Pirie," John Burdon Sanderson Haldane," *Biog. Mem. Roy. Soc., 12* (1966), 219—249.

8. T. H. Morgan, "Genetics and the Physiology of Development," *Amer. Nat., 60* (1926), 489—515. For further discussion on the enzyme theory of the gene see A. W. Ravin, "The Gene as a Catalyst; The Gene as Organism," *Stud. Hist. Biol., 1* (1977), 1—45; and L. E. Kay, "W. M. Stanley's Crystallization of the Tobacco Mosaic Virus," *Isis, 77* (1986), 450—472.

their studies predisposed them to the view that in general there was a one-to-one correspondence between gene and enzyme — a view that motivated Beadle's future investigations.[9]

Beadle's success with the biochemical genetics of *Drosophila* was a limited one, however; there were major gaps in the biochemical pathway leading from the eye-color gene to the pigment, or end product. As Sturtevant wrote in a review article, referring to Beadle and Ephrussi's transplantation experiments, "The chain of developmental reactions may be traced back to the gene, but there is no way of determining when one has reached the gene."[10] Yet in spite of its incompleteness, geneticists considered Beadle's work to be a major contribution to biological knowledge. Leading American researchers in the life sciences regarded it as the first rigorous and systematic approach to the dilemma of how to get from the formal level of genetics to the level of physiological processes; the first disciplinary link between genetics and biochemistry in America. These important interdisciplinary studies accelerated Beadle's career, and after a year of lectureship at Harvard, he was offered in 1937 a permanent position at Stanford University. His accomplishments also brought him to the attention of the Rockefeller Foundation officers, the talent scouts for the new molecular biology program; in their report following a visit to the 1936 summer meeting at Woods Hole they rated Beadle as one of the most brilliant biologists of his generation: "A man to be watched."[11]

The keen interest of the Rockefeller Foundation in Beadle's work was crucial to his subsequent scientific endeavors; and this interest extended beyond financial support. According to the foundation's officers, they were responsible for putting Beadle in touch with Edward Tatum, a young biochemist from Madison, Wisconsin, and son of the noted Wisconsin biochemist Arthur L. Tatum. The senior Tatum, who was a powerful liaison between academic life sciences and the pharmaceutical industries, turned out to be a fortuitous connection for Beadle's later applied work in biochemical genetics.[12] Young Tatum, too, was a product of

9. B. Ephrussi and G. W. Beadle, "A Technique of Transplantation for Drosophila," *Amer. Nat., 50* (1936), 218–224; and B. Ephrussi, "Chemistry of 'Eye Color Hormones' of Drosophila," *Quart. Rev. Biol., 17* (1942), 327–338.

10. A. H. Sturtevant, "Physiological Aspects of Genetics," *Ann. Rev. Physiol., 3* (1941), 41–56.

11. F. B. Hanson Diary, September 4–5, 1936, Rockefeller Archive Center (hereafter RAC) RG 1.1, 205D, Box 7, File 88.

12. For the University of Wisconsin connection to the pharmaceutical industries and Arthur Tatum's role see J. P. Swann, "The Emergence of Cooperative Research between American Universities and the Pharmaceutical Industry, 1920–1940," Ph.D. diss., University of Wisconsin–Madison, 1985, chap. 5.

Wisconsin's biochemical tradition. A specialist in the chemistry of growth factors and nutrition in microorganisms, he had been trained in a biochemistry department closely tied to commercial nutrition research and the dairy industries. He had no prior exposure to genetics, but in joining forces with Beadle at Stanford, he brought to gene research the experimental approach and the techniques from nutrition and microbiology, as well as a link to the food and drug industries.[13]

The application of techniques from nutrition to the studies of biochemical genetics in *Drosophila* soon proved to be of diminishing returns: the biochemistry of the fly was far too complex, and the experimental results were becoming increasingly erratic. It was obvious that if progress were to accelerate a simpler organism had to be found and a different approach was needed. According to Beadle, he hit upon the idea of using the bread mold *Neurospora* while auditing one of Tatum's lectures in biochemistry sometime in 1940. It occurred to Beadle then to reverse the experimental procedure. Instead of starting from the gene end — from a known mutation — and then working toward the biochemical product (as he had done in the transplantation experiments), why not start from the biochemical end — from a known biochemical reaction — and then work backward to the gene? With the biochemical end already worked out, Beadle reasoned, he could then capitalize on his skills as a geneticist and stick to his specialty, as he put it. This reverse approach required working with a biochemically well-defined biological system, and well-characterized genetic mechanisms that were reasonably easy to analyze and control. One could then induce random mutations that would block biochemical reactions in the organism's metabolic pathways. A biochemical reaction could then be readily identified, and linked to the specific mutation associated with it. *Neurospora* seemed to fit these requirements exceptionally well.[14]

Beadle's idea of using *Neurospora* for his studies in biochemical genetics was not entirely fortuitous. He had been exposed to *Neurospora* research since his Cornell days, and had followed closely Carl Lindegren's doctoral project in *Neurospora* genetics

13. Various aspects of the growth of biochemistry and nutrition research at the University of Wisconsin are discussed in Rosenberg, *No Other Gods*, pp. 153—172. Additional sources are given in D. Bearman, J. Edsall, and R. E. Kohler, *Archival Sources in Biochemistry and Molecular Biology* (Philadelphia: American Philosophical Society, 1980), pp. 10—12. See also E. V. McCollum, *A History of Nutrition* (Boston: Houghton Mifflin, 1957), passim.

14. Beadle, "Recollections," p. 8; and G. W. Beadle, *Genetics and Modern Biology* (Philadelphia: American Philosophical Society, 1963), p. 13.

at Caltech in the early 1930s. Beadle was well aware of the advantages of that microorganism in genetic research. The haploid cells of the fungus (possessing only a single set of genes), in which complications associated with dominance did not arise, and its relatively short life cycle of ten days between sexual generations made the mold attractive for genetic analyses. The sexual union of two haploid cells from opposite mating types produced a zygote that, following the two meiotic divisions, produced four haploid cells, each of which then divided by mitosis. As a result, eight genetically identical spore cells were neatly lined up according to their closeness of lineage, in a spore sac, a feature that facilitated an orderly analysis of the gene sequence. With a microscope, a technician — or in Beadle's words, a "spore isolator" — could isolate a spore sac, remove the eight spores in sequence, and place each into a tube with culture medium. The spores would then undergo rapid asexual reproduction, yielding a large population derived from a single chromosome set. The uniformity and rapid yield had clear advantages over the complicated pattern of reproduction in *Drosophila*.[15] (see Fig. 1 on next page)

Beadle obtained stocks of *Neurospora* from Lindegren, and Tatum performed the biochemical characterizations of *Neurospora* metabolism. Applying his expertise in the biochemical nutrition of fungi, Tatum worked out within a few months the normal nutritional requirements of the organism. Its diet turned out to be exceedingly frugal: all species of the fungus could grow on a minimal medium containing sugar, salts, and biotin (one of the B vitamins); that is, the mold could synthesize all its required substances out of the ingredients in the minimal medium.

On the basis of the lessons learned from the transplantation experiments in *Drosophila* about the relation of mutant genes to synthetic steps along a biochemical pathway, Beadle designed his experimental strategy for *Neurospora*. He reasoned that if a mutant gene manifested a loss of a particular synthetic step, then that mutant *Neurospora* would be unable to synthesize some essential substance and would thus fail to grow on minimal, or unsupplemented, medium. By finding out which nutrient was needed for survival, a correlation could then be established between the mutant gene and the organism's failure to survive as a result of the blockage of a particular synthetic step along a metabolic pathway. From the biochemistry of the pathway, one could then match, so to speak, a specific synthetic step with a

15. *Nobel Lectures*, p. 356; and G. W. Beadle, "Genetics and Metabolism in Neurospora," *Physiol. Rev.*, *25* (1945), 643–663.

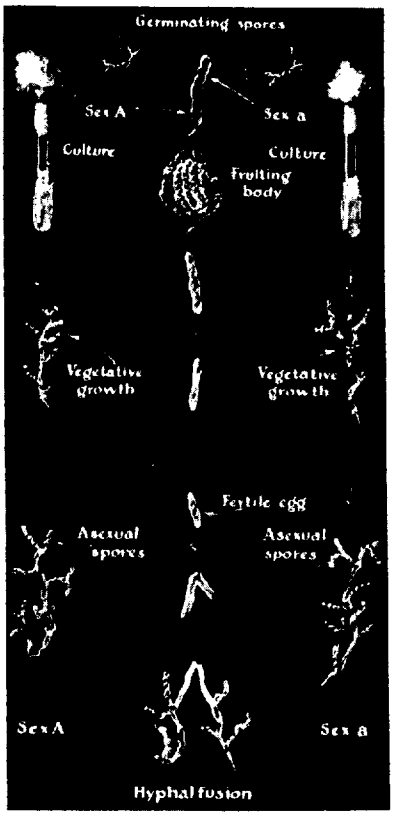


Fig. 1. Life cycle of *Neurospora*. The hyphal fusion of opposite mating types Sex A and Sex a at the bottom is taken as the starting point. The fusion results in a zygote, in which two complete sets of genes are paired. The zygote divides twice to produce four nuclei, each of which has only a single set of genes (center). Lined up in a spore sac, the four nuclei divide once more to produce four pairs of nuclei that are genetically identical. A group of spore sacs is gathered in a fruiting body. The sacs and the spores are dissected by the techniques outlined in figs. 2 and 3. (From G. W. Beadle, "The Genes of Men and Molds," *Scientific American, 179*, no. 3 [1948], 33.)

particular mutant gene. The experimental design was elegant in its simplicity; irradiate the asexual spores of the mold with X rays to produce random mutations then cross the irradiated spores with the appropriate mating type, isolate newly reproduced spores, grow them on a suitably supplemented medium, and test them on the unsupplemented medium. (see Fig. 2 and Fig. 3.) With exceptionally good luck, a few months later Beadle and Tatum isolated a first X-ray *Neurospora* mutant. "I always knew they were fine bugs to work with," Beadle wrote to Lindegren in July 1941, "but I never fully appreciated all their advantages. We have one X-ray

mutant that seems not to be able to make one of the B-vitamins but we haven't yet finished the analysis of this."[16]

By October 1941, in the *Proceedings of the National Academy of Sciences* Beadle and Tatum reported having isolated three mutant strains of *Neurospora*. One was unable to synthesize vitamin B_1; the second was unalbe to synthesize B_6; and the third, para-aminobenzoic acid. The preliminary results indicated that *Neurospora* offered a very effective genetic system for analysis, and that the new research methods could indeed be used to isolate mutants that were unable to carry out a particular step in a given synthesis, and thus to determine "whether one gene is ordinarily

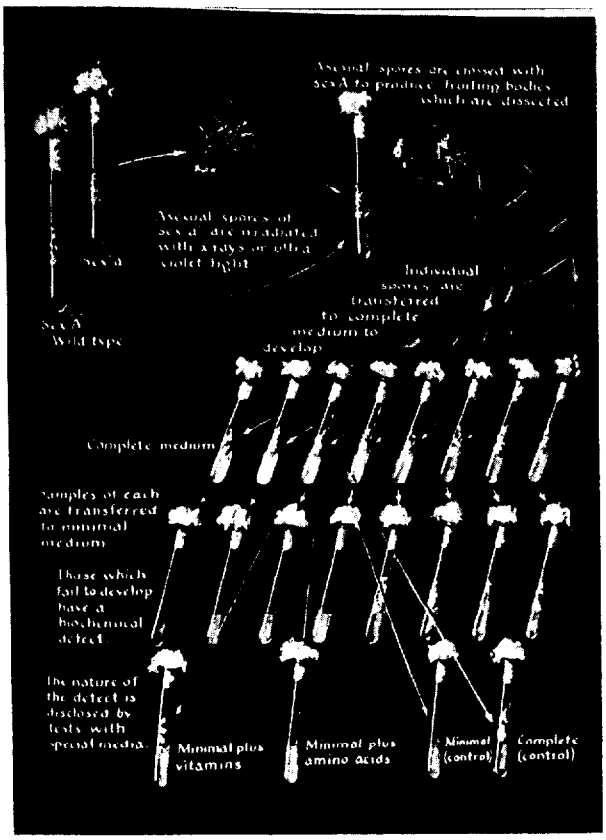


Fig 2. An experiment to determine a single defective gene in *Neurosopra*. (From G. W. Beadle, "The Genes of Men and Molds," *Scientific American, 179*, no. 3 [1948], 35.)

16. Beadle to Lindegren, July 25, 1941, California Institute of Technology Archives (hereafter CIT), *Beadle Papers*, Box 1, File 49.

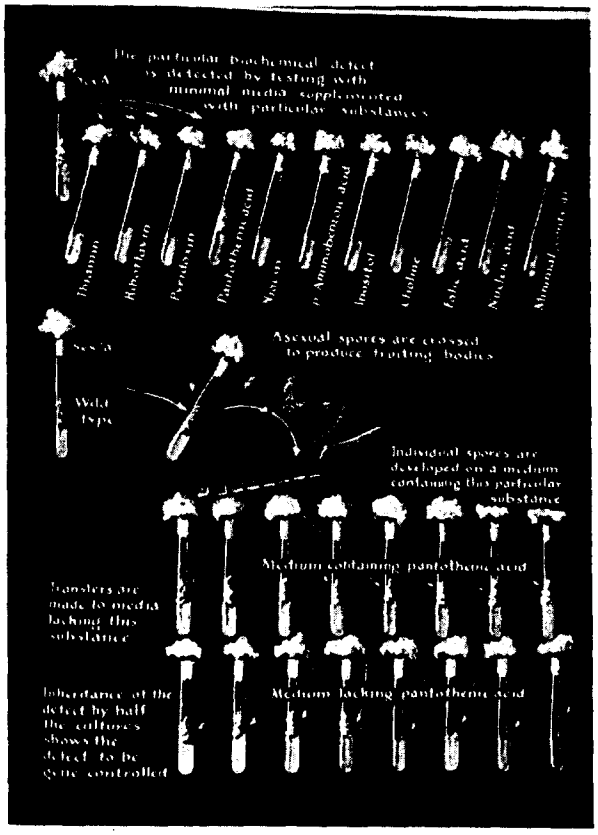


Fig. 3. The strain of *Neurospora* that carries a defective gene is subjected to a series of tests in order to determine the specific biochemical deficiency associated with the defect. (From G. W. Beadle, "The Genes of Men and Molds," *Scientific Americans, 179*, no. 3 [1948], 37.)

concerned with the immediate regulation of a given specific chemical reaction." That information, Beadle predicted, would reveal the mechanisms by which genes regulate development and physiological functions.[17] The theoretical import of these findings was far-reaching, and the potential of the new experimental system for fundamental biological knowledge was immense. Even before its publication in the *Proceedings*, upon reading the manuscript, Ephrussi immediately wrote to Beadle: "I want to congratulate both you and Tatum. I believe that these first results leave no doubt that you are entering an unexplored field of most promising possibilities."[18]

17. G. W. Beadle and E. L. Tatum, "Genetic Control of Biochemical Reactions in Neurospora," *Proc. Nat. Acad. Sci., 27* (1941), 494–506.

18. Ephrussi to Beadle, August 22, 1941, CIT, *Beadle Papers*, Box 1, file 26.

II. APPLIED BIOCHEMICAL GENETICS AND THE DEMANDS OF WAR

The potential applied aspects of the new research were not disregarded. Even in their preliminary report Beadle and Tatum were quick to stress the practical significance of *Neurospora* biochemical genetics, and its utility to other areas such as nutrition and pharmacology. The methods outlined, they argued in their 1941 paper, were of value as techniques for discovering additional substances of physiological significance. A complete medium could be made up with extracts of normal *Neurospora*, and if through mutations the ability to synthesize some substance were lost, it could then serve as a test strain for isolating the substance. "It may of course be a substance not previously known to be essential for the growth of any organism," they suggested. "Thus we may expect to discover additional amino acids if such exist."[19] This was a bold assertion; undoubtedly, the increasing attention to commercial and military needs had some influence on Beadle's research strategy.

At that time — 1941 — the United States was at the height of its "preparedness" phase. A vigorous campaign to reorganize the nation's scientific resources for the demands of war had been launched by several leaders of the scientific establishment: Frank Jewett, James Conant, Vannevar Bush, and Karl Compton, whose efforts had resulted, by the summer of 1940, in an executive order to establish a National Defense Research Committee (NDRC). The purpose of the NDRC was to contract with educational institutions, scientific organizations, individuals, and industries in order to coordinate war-related research. A second executive order in the summer of 1941 created, under Bush's directorship, the Office of Scientific Research and Development (OSRD), and endowed it with resources and powers to initiate and coordinate research beyond those of any previous coalition of science, industry, and the military.[20]

Within the OSRD, the Committee on Medical Research (CMR) had just been assembled under the leadership of Alfred N. Richards. A leading pharmacologist at the University of Pennsylvania School of Medicine, Richards, like Arthur Tatum, was an

19. Beadle and Tatum, "Genetic Control," p. 505.

20. Irvin Stewart, *Organizing Scientific Research for War* (Boston: Little, Brown, 1948); J. P. Baxter, III, *Scientists against Time* (Boston: Little, Brown, 1946); R. G. Cochrane, *The National Academy of Sciences* (Washington, D. C.: National Academy of Sciences, 1978), pp. 382–432; D. Greenberg, *The Politics of Pure Science* (New York: The New American Library, 1967); and chap. 1 in D. F. Noble, *Forces of Production* (New York: Knopf, 1984).

influential figure in the pharmaceutical industries, and a major consultant for Merck and Company.[21] The purpose of CMR was to develop and coordinate war-related projects in several academic and commercial fields of the life sciences. The medical fields encompassed researches on malaria; infectious, venereal, and tropical diseases; convalescence; neuropsychiatry; various aspects of surgery; and aviation medicine. Research projects in physiology included the areas of nutrition, acclimatization, and water sterilization; the physiology of shock; the development of blood substitutes; and agents for boosting resistance to disease — both drugs and vaccines. Within the field of chemistry, insect and rodent control and gas poisons comprised two major areas; biochemical research concentrated mainly on adrenal cortical hormones, and on the production of penicillin. Many of the war projects in pharmacology and biochemistry, notably the production of penicillin, were being coordinated with the Department of Agriculture and with commercial concerns such as the pharmaceutical firms of Merck and Company, E. R. Squibb and Sons, Sharp and Dohm, and the Lederle Laboratories.[22]

In 1941, just when Beadle and Tatum were publishing their preliminary results on *Neurospora* and pointing out the work's projected practical applications, nonessential scientific expenditures were being trimmed back. Most researchers in the physical sciences had already organized their war-related projects under the auspices of the OSRD. Investigators in the life sciences, in areas relevant to the priorities outlined by CMR, were increasingly entering into government contracts, which were usually drawn for six to twelve months. Basic research in the life sciences was being gradually curtailed.

For Beadle however, the *Neurospora* program was just beginning. He envisioned a large-scale attack on the fundamental problem of the relation between genes and enzymes, work that was both time-consuming and expensive. The laborious task of running mutants through what he called a "nutritional mill" — that is, through a systematic battery of tests for various vitamin and amino acid deficiencies — required many hands and substantial sums for materials. The projected research program called for expanded laboratory facilities and staff. As Beadle explained in his 1941 grant proposal to the American Philosophical Society, 34,000 *Neurospora* strains had been established and tested in the previous year; each strain, in turn, had resulted in several cultures;

21. Swann, "Emergence of Cooperative Research," chap. 4.
22. Stewart, *Organizing Scientific Research*, chap. 7.

and out of these hundreds of thousands of cultures, only 102 mutants had been isolated so far. In requesting additional funds, Beadle explained that it would take 20,000 tries to find a single additional mutant. Yet the value of each additional mutant, he argued, increased as the list approached completeness, because when matched with the corresponding chemical reaction, these last mutants would fill in the crucial remaining pieces of the biosynthetic puzzle.[23]

Beadle also appealed to the Rockefeller Foundation for additional support. In November 1941, a month after the first publication on *Neurospora*, he wrote to Warren Weaver, director of the foundation's Division of Natural Sciences. After explaining to Weaver some of the difficulties with the new experimental procedures, he reported that since the initial report he and Tatum had more than doubled the number of mutants having a known role in synthesis. Among the newer mutants, one had been found that lacked the ability to synthesize what appeared to be a new, unknown amino acid, which they had named neurosporin.[24]

While progressing on the basic research front, Beadle was also being courted by the food and drug industries; genetics was making unexpected contributions to the science of nutrition. Aside from their theoretical significance, a number of the newly isolated mutants that were unable to synthesize either a vitamin or an amino acid had proved to be important in applied bioassay work. The growth rate of each mutant was a function of the concentration of the substance in which it was deficient. Therefore, by measuring the dry weight of the mycelium (the vegetative form of the fungus) produced during a specified growth period, or by following the rate of progression of the mycelial frontier over the agar surface, one could obtain an estimate of the concentration of the specific substance in the medium. One of the advantages of *Neurospora* techniques as compared with other methods, according to Beadle, was the efficiency and specificity of response. The *Neurospora* bioassays were therefore attractive procedures for commercial houses that dealt with the manufacture of vitamins and amino acids.[25]

From the point of view of the Rockefeller Foundation, links between basic research and its commercial exploitation could potentially create delicate situations. Because the Natural Sciences

23. Beadle to Eisenhart, December 21, 1941, CIT, *Beadle Papers*, Box 3, file 5.

24. Beadle to Weaver, November 28, 1941, CIT, *Beadle Papers*, Box 2, file 54.

25. Ibid.

Division supported basic, nonmedical research, questions of practical applications and patent rights were of only marginal concern to it; that division therefore had no firm guidelines in respect to commercial ties between academic research and industry, and usually left such matters to the discretion of individual investigators. The Medical Sciences Division, on the other hand, did have an explicit policy regarding these ties. Because of the obvious connections between biomedical research and clinical applications (including drug manufacturing), the medical division discouraged applications for patents on the products of research supported by the foundation. In cases of overlapping interests, when the results of basic research done under grants funded by the Natural Sciences Division were of pharmacological or medical utility (as in Beadle's case), the matter of patents was ambiguous.[26] Thus while Beadle stressed in his report to the Rockefeller Foundation the immediate practical value of the *Neurospora* mutants as offering a new assay method for food and drug testing, he also solicited Weaver's advice regarding commercial involvements.

In November 1941 Beadle told Weaver that Merck and Company had expressed an interest in supporting *Neurospora* research. Because of the efficacy of the new analytic and culturing techniques and the precision of the vitamin and amino acid assay methods, the company was enthusiastic about entering into collaborative research with Beadle's laboratory. Of course his laboratory could benefit a great deal from cooperative ventures with Merck and similar concerns, Beadle wrote to Weaver — but he was uneasy about linking his research program with the work of pharmaceutical houses. He felt that there were definite disadvantages in ties with commercial concerns due to the possibility of disagreements over such questions as manufacturing procedures and patent rights in relation to newly discovered substances. He would prefer to limit such entanglements.[27] Since the Natural Sciences Division of the Rockefeller Foundation had no clearly articulated policy in regard to patents, the officers stated that they had no intrinsic objections to Beadle's entry into applied research, and left the matter up to him.

A month later Beadle visited Merck and Company in New Jersey in order to explore the possibilities for cooperative projects. He learned that Merck was willing to support the entire *Neurospora*

26. Hanson to Pauling, June 8, 1942, RAC, RG 2.2, 205D, Box 7, file 93. Foundation officer Hanson explained this patent issue to Pauling in respect to the immunology project at Caltech, since that project combined the interests of the Natural Sciences and Medical Sciences Divisions of the Rockefeller Foundation.

27. Beadle to Weaver, November 28, 1941.

project in return for the patent rights. According to the report of the Rockefeller Foundation after Beadle's visit to New York in December 1941, Beadle was completely uninterested in the patent question and, in fact, the patent policy of Stanford University seemed to be opposed. The foundation officer reported that Merck would probably be willing to supply funds and assistance without any patent rights; but in return for furnishing the chemical services they would expect to obtain information in advance of publication of any papers, and thus to acquire an edge on their competitors. The Research Corporation was also interested and led Beadle to believe there were considerable chances for the success of an application to it, unless there were complications due to patent problems. The Rockefeller Foundation officer noted: "Beadle states explicitly that he has no interest in patent nor any personal profit for himself but, on the other hand, must find outside assistance to push this work rapidly. His first preference would be a grant from the RF which would free him of all obligations other than to work hard and publish freely his results. His second choice would be the Research Corporation and third, Merck."[28]

In 1942 Beadle received a grant from the Rockefeller Foundation, but he also entered into cooperative projects with Merck and Company, and later with Sharp and Dohm and other commercial agencies. In 1943, the Research Corporation, which had very close ties with the OSRD and heavily supported work on nutrition (particularly the nutrition research at Wisconsin), awarded Beadle $10,000. Beyond this financial support, Beadle undoubtedly benefited from other services of the Research Corporation, which the Rockefeller Foundation (and other agencies) often used to "hold" patents that were licensed to commercial houses.[29]

The early links between *Neurospora* research and the food and drug industries not only broadened Beadle's financial and institutional base, but also carried considerable weight in assessing the utilitarian value of his program. These connections were a testimony to the practical significance of the work at a time when relevance to nutrition and pharmacology counted for much. When Beadle reapplied for a Rockefeller Foundation grant for 1942, Stanford's president R. Wilbur not only praised the *Neurospora*

28. Hanson's report, December 15—18, 1941, RAC, RG 1.1, 205D, Box 19, file 191.

29. Beadle to Hanson, April 3, 1943, RAC, RG 1.1, 205D, Box 10, file 143. Also Beadle, "Recollections," pp. 1—13.

program as "ushering a new era in genetics research," he also promoted the broad range of practical applications. "The wide scope of the problems on which these researches bear," Wilbur wrote to the Rockefeller Foundation's president Raymond Fosdick, "gives them an importance not only for further advancement along these [genetics research] lines but also for more immediate applications in our present war emergency. The latter aspect alone would seem to justify an additional grant from the Rockefeller Foundation."[30]

Indeed, the grant that the Rockefeller Foundation appropriated in 1942 for basic research in biochemical genetics was reinforced by a grant for fundamental studies of *Neurospora* from the American Philosophical Society, and buttressed by the various benefits of collaborative projects with the food and drug industries — which by 1942 included Merck, the Fruit Products Laboratory, and the Western Regional Department of Agriculture. Clearly Beadle attached a great deal of weight to the practical and commercial side of *Neurospora* work, while simultaneously pursuing his main interest: the correlation between mutant genes and their biochemical deficiencies.[31]

This twofold approach to *Neurospora* research — the pure and the applied — and the broad base of support it attracted resulted in a considerable expansion of Beadle's program. His applied work was in great demand, and several laboratories began sending people to Stanford to learn the new techniques. Beadle also gathered junior faculty members, postdoctoral fellows, graduate students, and additional technicians. Of the new investigators who joined Beadle's group in 1942, Norman Horowitz and David Bonner from Caltech were particularly valuable to the development of the new biochemical genetics. Having studied in the 1930s in Morgan's interdisciplinary division, they were the first generation of American graduates trained in the new physicochemical biology. Both were proficient in genetics as well as in biochemistry, and possessed for the early 1940s, a unique combination of skills to bring to *Neurospora* research. Upon inviting his Caltech friend Sterling Emerson to spend the summer of 1942 at Stanford, Beadle described the rapid growth of his group and boasted: "We have up our sleeves plans for a super gigantic Neurospora Institute for next summer."[32]

By the summer of 1942 the United States was deeply involved

30. Wilbur to Fosdick, December 19, 1941, RAC, RG 1.1, 205D, Box 10, file 141.

31. Beadle to Hanson, February 20, 1942, CIT, *Biology Division Records, 1936–1946*, Box 11, file 1.

32. Beadle to Emerson, March 14, 1942, CIT, *Beadle Papers*, Box 2, file 53.

in the war, and science had become heavily immersed in the war effort. Laboratory resources had been diverted toward war-related projects, and junior laboratory personnel were being drafted into the armed forces. Senior researchers, even those who discontinued basic research, were experiencing difficulties in maintaining post-doctoral fellows, graduate students, and technicians. The future of many research programs in the life sciences now became uncertain — a situation that presented special problems to the Rockefeller Foundation regarding its annual appropriations allocated to long-term grants awarded before the war. As part of a general survey, the foundation requested information from its principal supported investigators concerning the war's impact, or projected impact, on basic research — on the availability of personnel, or the acquisition of materials and equipment. The foundation expressed its preference for maintaining those basic and long-term research programs that could be sustained on a high level without conflicting with the demands of defense. However, the officers did not wish to see the quality of research compromised because of the exigencies of war, or due to time constraints; wherever and when disruption did occur, they felt, it might prove necessary to reduce the level of support, or even to terminate it.[33]

In the spring of 1942 Beadle still emphasized his primary commitment to basic research, but the pressures of military relevance had already begun to manifest themselves. He wrote to the Rockefeller Foundation:

> Our facilities and the generous Foundation support are proving to be quite adequate for the basic aspect of the work and I feel confident that we shall continue to make satisfactory progress along these lines. It becomes increasingly evident, however, that it is desirable to apply these findings to the development of a rapid standardization technic of bioassay for various vitamins and amino acids. While it seems obvious that this type of work should not be done at the sacrifice of more fundamental work, it occurred to us that a number of our best qualified graduate students, who are actively looking for ways to be useful in the present emergency, might well undertake such applied work with a view toward making efficient bioassay technics available for studies of vitamin and amino acid contents of various types of preserved foodstuffs.[34]

33. Hanson to Pauling, January 21, 1942, RAC, RG 1.1, 205D, Box 7, file 85. In requesting a similar assessment of Pauling's project in immunochemistry, the officer explained the nature and purpose of the foundation's general survey.

34. Beadle to Hanson, April 15, 1942, RAC, RG 1.1, 205D, Box 10, file 142.

Beadle inquired about the Rockefeller Foundation's reaction to his proposal that the Nutrition Foundation, Inc., founded by fifteen national manufacturers and headed by Karl T. Compton, might support four graduate fellowships at Stanford University for two years. Following the approval of the Rockefeller Foundation, the Nutrition Foundation awarded Beadle a substantial sum for fellowships and equipment. This support further facilitated the applied aspects of Beadle's *Neurospora* program.[35]

Up until the summer of 1942, Beadle had been able to hold on to his men and to ensure the continuity of his program. He had relied on the argument that considering the importance of adequate protein nutrition during times of meat shortages, it was of great practical as well as theoretical importance to complete the amino acid mutant list. Because of the projected meat shortages, and because California's agribusiness was the nation's principal supplier of produce, Beadle had buttressed his argument by promoting the new assay techniques. The *Neurospora* assay methods for determining the vitamin content in produce, and the means of creating "high vitamin" products, were at a premium, he claimed. "This question of the vitamin content of dehydrated products will certainly become increasingly important in the near future from both military and civilian stand point. We feel that we should very soon know just how useful 'made-to-order' *Neurospora* mutants will be in vitamin research and control."[36] His arguments remained effective until mid-1942.

In the summer of 1942 the Local Board denied his requests for military deferments for his graduate students and assistants. Beadle was about to lose a couple of his men and basic *Neurospora* research was now threatened by the demands of the war. Beadle informed the Rockefeller Foundation about the new developments. Soliciting their cooperation, he asked that they intercede on his behalf and use their influence with the Local Board and State Appeal authorities. He suggested that the deferment of men who had training and skills in the biochemical genetics of *Neurospora* could be justified on the ground that their contributions to the field of nutrition were likely to be much greater than any contribution they could make when starting from the ground up, in

35. Ibid.

36. Beadle to Hanson, February 20, 1942, CIT, *Biology Division Records, 1936–1946*, Box 11, file 1. For the rise of California's agribusiness see W. Bean and J. J. Rawls, *California: An Interpretive History* (New York: McGraw-Hill, 1982).

direct military service.[37] The Foundation decided, however, as a matter of policy, not to exert pressure upon Local Boards.[38]

The Rockefeller Foundation's decision to avoid intervention in military matters naturally accelerated the trend toward applied *Neurospora* research. Although Beadle reacted very graciously to the foundation's refusal by stating that he could see "how a stand other than the one taken would be difficult to maintain as a general proposition," he also communicated his resolve to intensify the practical direction of biochemical genetics as a result of war time pressures. "Several of us at Stanford feel," he wrote, "that it is becoming more and more obvious that the only way we are going to be able to continue scientific work is to turn our efforts more and more toward applied lines. Even so, contracts with governmental agencies would still be essential to the survival of research groups."[39] Accordingly, Beadle's team would now begin exploring the possibilities of obtaining one or more contracts in connection with the development of vitamin and amino acid assays.

A few months later, Beadle flew east to meet with the Subcommittee on Medical Nutrition of CMR in order to investigate the possibility of using some of his laboratory facilities and techniques to study problems of nutrition related to the war effort. As a result of these meetings it was agreed that Beadle's *Neurospora* program could aid several ongoing CMR projects. Although the group's research would not be performed under government contract, it was concluded that *Neurospora* techniques and results should definitely aid the work of R. J. Williams at the University of Texas on para-aminobenzoic acid, the Harvard project on tetanus, and E. N. Ballantyne's project on gas gangrene. Beadle emphasized that he still planned to push forward in basic research, but that new weight would now be given to applied war research.[40]

In the following month, November 1942, Beadle's program of biochemical genetics was classified as essential to the war effort under the CMR guidelines, though it did not receive a formal contract. Beadle immediately dispatched a letter to the Rockefeller Foundation in which he quoted with obvious pride, excerpts from Richards's letter:

37. Beadle to Hanson, July 3, 1942, RAC, RG 1.1, 205D, Box 10, file 142.
38. Hanson to Beadle, July 7, 1942, ibid.
39. Beadle to Hanson, July 13, 1942, ibid.
40. Beadle to Hanson, September 17, 1942, and Hanson's report, October 14, 1942, ibid.

> This is equivalent to saying that it is my conviction, which I am confident would be shared by all other members of the committee, that the work is of sufficient fundamental importance and potential practical usefulness that it should not be interrupted in favor of other research which may seem to have more immediate practical utility in the War Effort. I can only assure you that we will endeavor to give such requests [deferments in the absence of government contract] the full influence of the Office of Scientific Research and Development in the case of any of your investigators whom you certify as essential and irreplaceable. Similarly in the case of critical materials for which high priorities are needed, we will do everything in our power to assist you.[41]

This official statement provided the necessary guarantee that Beadle's program of biochemical genetics would develop relatively unhindered. In fact, by having no formal contract, Beadle gained an advantage: he was free to pursue his work with fewer constraints on his facilities and time, while receiving priority privileges equivalent to contracted research. He could also publish freely. "Naturally we are encouraged by this letter," Beadle wrote [to the Foundation's] officer F. B. Hanson: "We feel that we can now go ahead with our work with clear conscience."[42]

During the war years Beadle's group isolated about 80,000 single spores; of these, approximately 500 had given rise to mutant strains that were unable to carry out essential syntheses, and over 100 mutant genes controlling vital syntheses had been detected. The majority of the mutants were characterized by loss of the ability to synthesize either a vitamin, or an amino acid, or a nucleic acid component. Mutants for the synthesis of seven B-complex vitamins and twelve amino acids were established, and most of these had been shown to be essential for rat, dog, and human metabolism. Using the *Neurospora* mutants, Beadle's groups had worked out bioassays for choline, para-aminobenzoic acid, inositol, pyridoxin, and leucine. With no constraints of the secrecy so inherent in classified contract work, and with no obligations to industry resulting from patent restrictions, Beadle and his collaborators were free to publish most of their findings in the standard scientific journals. The numerous articles and reports about the culture techniques needed for mutants, and about the various bioassays the group had developed, appeared in the *Journal of*

41. Beadle to Hanson, November 6, 1942, p. 1, ibid.
42. Ibid., p. 2.

Biological Chemistry, the *American Naturalist, Physiological Reviews*, the *American Journal of Botany*, the *Journal of Bacteriology*, and the *Proceedings of the National Academy of Sciences.* These publications made Beadle's research highly visible during wartime.[43]

Not all that Beadle touched turned to gold. At the end of 1942, he communicated to the Rockefeller Foundation his belief that the putative new amino acid neurosporin had been isolated, and furthermore, that it promised to be of importance in CMR's tetanus toxin project. There was a great deal of excitement and a flurry of activity in the laboratory as "Tatum and Bonner," according to Beadle, were "burning the night lights trying to get the structure established and a synthesis worked out."[44] But soon afterwards, Beadle had to retract the discovery. Disappointed, he reported to the Rockefeller Foundation that what for some time was thought to be the new amino acid neurosporin had actually turned out to be an active crystalline material isolated from a casein hydrolysate; neurosporin was actually a mixture of valine, isoleucine, and leucine. Although still useful as a booster in the preparation of tetanus toxin, the new substance was only of marginal fundamental significance.[45]

The "false" amino acid was but a minor setback. The profundity of Beadle's program lay in its contributions to fundamental biological knowledge — in elucidating the relation of individual genes to individual metabolic reactions and, in turn, to the specific enzymes regulating these reactions. Without exception, every biochemical pathway leading to the synthesis of a final product — either a vitamin or an amino acid — proved to be comprised of a series of biochemical reactions. In each case, a specific gene mutation blocked only a single biochemical reaction along the pathway, and by inference, depended on the deficiency of a specific enzyme.

The detail involved in analyzing the sequence of biochemical steps in a synthetic pathway was staggering, scores of *Neurospora* mutants being needed for a single step. Several of the pathways under study therefore contained gaps. But two important biochemical sequences and their corresponding mutants had been well characterized by the end of the war. Horowitz and his collaborators established that the synthesis of the amino acid arginine in *Neurospora* proceeded through the synthesis of two precursors, ornithine and citrulline, and that each step in the sequence of

43. Beadle's report, "Genic Control of Biochemical Reactions in Neurospora," December 2, 1944, RAC, RG 1.1, 205D, Box 10, file 144.

44. Beadle to Hanson, November 24, 1942, ibid., file 142.

45. Beadle to Hanson, January 27, 1943, ibid., file 143.

reactions was under genic control (thus by inference, under the control of a specific enzyme). Furthermore, by working out the reaction cycle, they showed that the biochemical reactions were identical to the ones occurring in mammalian liver. The same experimental approach was used to study the synthesis of the amino acid tryptophan. Bonner and his associates showed that anthranilic acid and indole were intermediate products in the synthetic pathway of tryptophan in *Neurospora* and that each was under specific genic control. These findings established for the first time a mechanism of tryptophan synthesis in organisms.[46] (see Fig. 4)

At the end of 1944, in a lengthy report to the Rockefeller Foundation in which he described the conceptual and technical

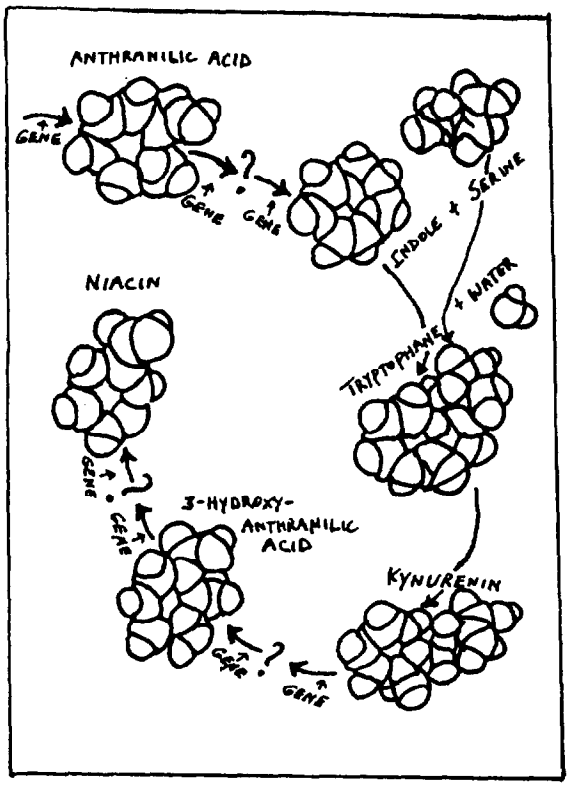


Fig. 4. The sequence of gene-controlled biochemical steps involved in the synthesis of the B-vitamin niacin from its precursor anthranilic acid. This sequence is also involved in pellagra. Drawing by author based on G. W. Beadle, "The Genes of Men and Molds," *Scientific American, 179*, no. 3 (1948).

46. Beadle's report, "Genic Control of Biochemical Reactions in Neurospora," pp. 10–11.

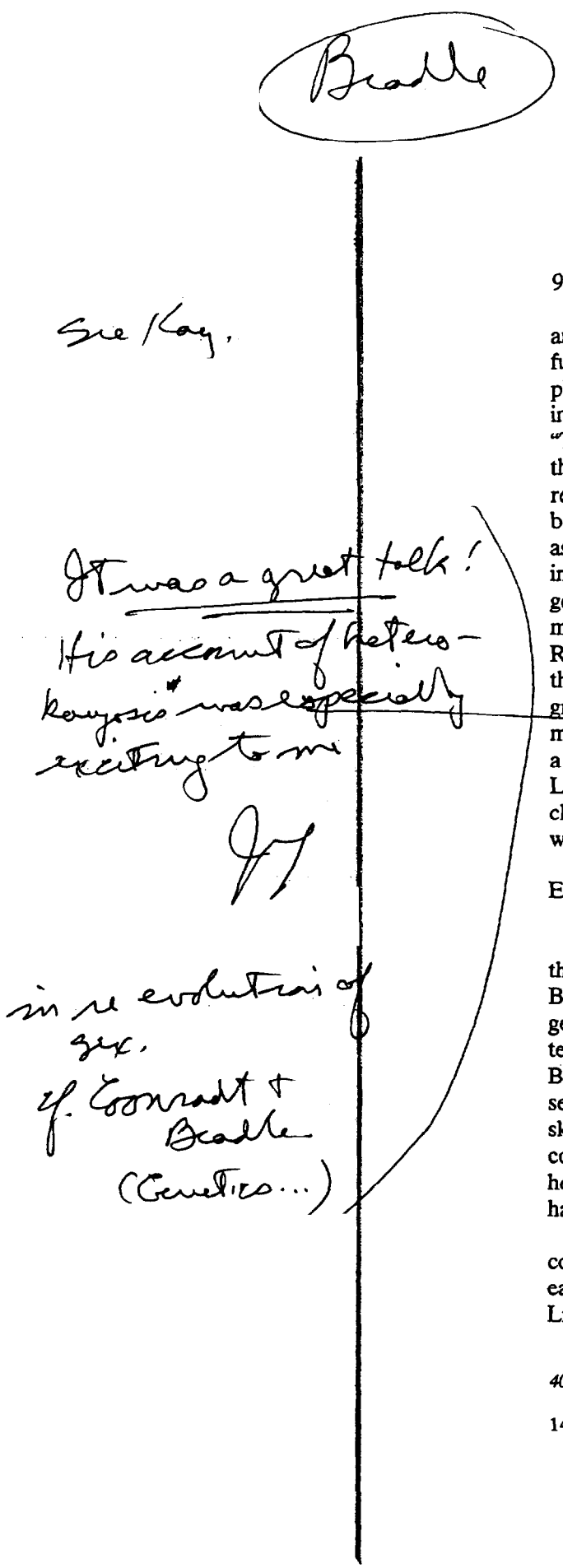
aspects of *Neurospora* research, Beadle presented two main conclusions. The first was that the synthesis of the essential constituents of living matter is under genic control, and that the requirements of higher animals for dietary supplements of vitamins and amino acids are the result of gene mutations that have occurred in the evolution of species. "Although it is going beyond our present information to suggest a mechanism of this control," Beadle cautioned, "it appears that the primary action of the gene has to do with the synthesis of the enzymes which direct the chemical activities of the cell." The second conclusion was that there exists a one-to-one correspondence between gene and chemical reaction. The studies of *Neurospora* mutants made it possible to assign definite series of reactions to individual members in a series of nonallelic genes. As Beadle had predicted in 1941, the reduction of gene effects to simple chemical reactions was indeed the first step in the direction of analyzing the physiological bases of gene action.[47]

During the last year of the war, direct military demands did indeed take some toll on Beadle's research program. In February 1944 he wired the Rockefeller Foundation that a representative of the War Production Board had just proposed that Beadle's group devote part of their facilities to inducing mutations in penicillium, in order to increase penicillin production. To do this would mean curtailing basic research activities for a while. Upon receiving the approval of the foundation, Beadle somewhat reluctantly embarked on the organization of the new project, which had little relation to *Neurospora* work, and which retarded the rate of progress of whatever basic research he had been managing to push forward. As young men were being drafted at an increased rate, he was also experiencing some difficulties in holding on to the men on his team. "I'm afraid one of the undesirable results of the war is going to be a missing generation of scientists," he wrote to the foundation, lamenting the attrition.[48]

Nevertheless, by 1944 the conceptual foundations of the *Neurospora* research program and the disciplinary merger of biochemistry and genetics were quite firm. Even though war-related activities had retarded the rate of progress, some additional fundamental research did get accomplished. By 1945, when the war ended, Beadle emerged as the leading authority in a new field that linked physiological processes, biochemical reactions,

47. Ibid. He also credited Sewall Wright with proposing some of the evolutionary interpretations.

48. Beadle to Hanson, January 17, 1944, RAC, RG 1.1, 205D, Box 10, file 144.



and genetic controls. As an astute discipline builder, Beadle was fully aware of the institutional innovations of his program, and he played up their importance in his lectures. When in 1945 he was invited to deliver that year's Harvey Lecture, he chose to discuss "The Genetic Control of Biochemical Reactions," and to promote the conceptual as well as the disciplinary accomplishments of his research program. Deploring the evident lack of interaction between genetics and biochemistry, he referred to that weakness as a "most unfortunate consequence of human limitations and the inflexible organization of our institutions of higher learning. The gene does not recognize the distinction — we should at least minimize it."[49] According to the testimony of the officer of the Rockefeller Foundation who attended Beadle's Harvey Lecture at the Academy of Medicine in New York, Beadle had received a great ovation. He concluded his lecture with the dramatic statement that up until recently, some students in the university entered a laboratory through a door on which was printed "Genetics Laboratory"; other students entered another door labeled "Biochemistry Laboratory"; but in the future, genetics and biochemistry were to be one subject.[50]

EPILOGUE AND CONCLUSION

Not all researchers in the life sciences responded favorably to the various innovative aspects of Beadle's research program. Beadle's criticism of the intellectual and institutional separation of genetics and biochemistry seemed to be partly a reaction to the tepid reception of his fundamental conclusions. According to Beadle, when in 1945 he traveled across the United States on a series of about twenty-four Sigma Xi lectures, he found many skeptics but few converts to the new interpretation that genes control enzymatically regulated chemical reactions. Even in 1951, he said, the believers could be counted on the fingers of one hand.[51]

Norman Horowitz recalled that despite the evidence to the contrary, many geneticists preferred to adhere to the old view that each gene was pleiotropic — that is, manifold in its action. Limiting the influence of hereditary determinants to merely regu-

49. G. W. Beadle, "Genetic Control of Biochemical Reactions," *Harvey Lect.*, *40* (1945), 193.

50. Hanson's report, February 15, 1945, RAC, RG 1.1, 205D, Box 10, file 145.

51. Beadle, "Recollections," p. 11.

lating intermediate chemical reactions along a pathway was tantamount to dethroning the gene. Some biochemists and physiologists felt that a microorganism was not representative of mammalian physiology, that the chemistry of *Neurospora* was too simple to prove a general rule. Several researchers denounced Beadle's hypothesis, on the basis that his methodology was unverifiable and unfalsifiable. Max Delbrück, for one, alleged that Beadle's conclusion was based on selection procedures that ensured that only mutations supporting the theory would be detected. Certainly the inference that followed after much detailed work, that a given gene controls the production of a single enzyme, was opposed. According to Horowitz, critiques published at the time were but pale shadows of the unpublished objections that were voiced in the 1940s and early 1950s at Cold Spring Harbor Symposia.[52]

Several salient features of Beadle's research were universally appreciated, however. The importance of the discovery of mutations that block the syntheses of vitamins and amino acids was generally acknowledged from the start. Beadle did succeed, at least partially, in blocking the circularity in the gene-enzyme dilemma of what genes are and what they do — whether genes are enzymes or only control reactions catalyzed by enzymes. The interdisciplinary innovations, the combination of theories and laboratory techniques from genetics and biochemistry, were certainly applauded by researchers in the life sciences, as well as by the officers of the Rockefeller Foundation. In 1944 Beadle was elected to the National Academy of Sciences, and after declining two prestigious professorships, he returned to Caltech as chairman of the biology division to become a principal architect of their molecular biology program.

In order to explain Beadle's rise to scientific leadership during the war, especially in view of the prolonged resistance to some of his conclusions, this paper has followed closely the growth of his research program at Stanford from 1940 to 1945. It has also examined Beadle's contributions to fundamental biological knowledge and his great productivity in biochemical genetics under the exigencies of war. This analysis of the intellectual as well as the administrative aspects of the program has revealed that Beadle was fully aware from the start of the commercial potentialities of his studies. He had pursued from the beginning a two-tiered approach to the biochemical aspects of gene action: the pure, and the applied. While he was primarily motivated by the question of

52. Horowitz, "Genetics and the Synthesis of Proteins," p. 257.

the relationship between genes and enzymes from a purely intellectual point of view, he promoted the practical relevance of *Neurospora* research to agriculture, nutrition, and pharmacology.

We have seen that *Neurospora*, because of its relative simplicity and minimal growth requirements, proved to be an effective system not only for pure biochemical genetics, but also for commercial applications. While investigators in the life sciences might have disagreed with Beadle's theoretical claims, few could argue with the practical results. The convenient culturing techniques and the reliable bioassays for amino acids and vitamins that Beadle and Tatum developed in the course of their investigations, made *Neurospora* a commercial asset. The products of research were attractive to the food and drug industries, especially to Merck and Company. Beadle made his laboratory facilities and his new techniques readily available to commercial agencies and engaged in collaborative projects with pharmaceutical houses. But his research did not suffer from patent restrictions, which left him free to publish most of his findings in the main journals of the life sciences. The interest of pharmaceutical industries in Beadle's work contributed to its prominence in the life sciences; the benefits of collaborative commercial projects widened the scope of his financial and institutional resources, and the freedom to publish guaranteed his visibility in the new field he had created.

Most importantly, the commercial applications of Beadle's research program played a pivotal role at a time when utility counted. During the war years the immediate and projected applications of *Neurospora* research fell within the domain of several projects in nutrition and pharmacology under the OSRD's Committee on Medical Research. Although Beadle did not obtain a formal government contract for a specific war project (except briefly during the last year of the war, for work on penicillin production), his research program, because of its practical significance, was classified as essential to the war effort. This informal classification worked to his great advantage. He was successful in most instances in obtaining deferments for his men, as well as supplies and equipment for his laboratory. But while his research received priority consideration, Beadle, unlike those who labored under government contracts, was not obliged to divert a substantial portion of his resources to projects unrelated to his research interests. Furthermore, due to the nature of the studies and to the fact that his research was not officially classified, he was able to communicate his results in print *promptly*. This advantage enhanced the wide hearing he received during the war years.

In examining the factors that contributed to Beadle's acclaim as

one of the principal actors in the rise of molecular biology, this paper has explored a neglected historical dimension: that of the linkage of biochemical genetics to industrial and military concerns; the ties between life science, industry, and the military would be further amplified during the postwar era. To be sure, the primary importance of Beadle's *Neurospora* research lay in its outstanding contribution to fundamental biological knowledge. However, that research program survived and flourished because Beadle developed his pure science during the war as a highly marketable product that was deemed indispensable to the war effort.

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